REMARKS

This amendment is responsive to the Official Action dated November 8, 2002.

A petition for extension of time is attached.

Claims 1 - 36 were pending in the application.

No claims were allowed.

By way of this amendment, claims 2 and 32 were canceled.

Accordingly, claims 1, 3-31, and 33-36 are currently pending.

Objection to the specification:

The disclosure was objected to at paragraph 0024 because it was unclear as to whether 37° was degrees F or degrees C. Applicant has amended the specification at the appropriate place to clarify the correct temperature scale. Withdrawal of the objection is respectfully solicited.

Objection to Claim 32:

The Examiner objected to claim 32 indicating that if claim 26 were found to be allowable, claim 32 would be objected to under 37 CFR 1.75 as being a substantial duplicate of thereof. The Examiner states that the only difference between claims 26 and 32 resides in the preamble, where the preamble of claim 26 requires a composition, and similarly the preamble of claim 32 requires an implant. According to the Examiner, the composition is inherently an implant and the implant is inherently a composition.

Claim 32 has been canceled. Favorable consideration of claim 26 is requested.

Claim objections under 35 USC §112, first paragraph:

Claims 1-7, 9-19, 21-24 and 26-36 were rejected under 35 USC §112, first paragraph as the specification does not adequately enable a person skilled in the art to make or use the invention as claimed.

The specification provides enablement for tissue that is decellularized and acylated with a ratio of acylating agent to wet tissue weight of about 0.001:1 to about 0.003:1.

Received from < 4012734447 > at 5/8/03 1:36:04 PM [Eastern Daylight Time]

The Examiner states that with respect to claims 33-36, the specification does not reasonably provide enablement for acylating tissue that is not decellularized.

The term "decellularized" has been added to claim 33.

Claim objections under 35 USC §112, Second paragraph:

Claims 1-36 were rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the invention.

With respect to claims 1, 21, 26, 32 and 36 the ratio of said acylating agent to wet tissue weight is about 0.003:1 or less is confusing as to meaning and scope.

Claims 2 and 32 have been canceled.

Corrections have been made to claims 1, 13, 21 and 26 to claim the appropriate disclosed ranges.

With respect to claims 8, 20 and 25, the lower limit of acylating agent was recited before the upper limit.

Corrections have also been made to claims 8, 20 and 25.

With respect to claim 3, the Examiner states that the use of the term "cryomilling" renders the claim indefinite.

The Applicant respectfully disagrees. The term "cryomilling" is defined in the description as follows:

> *"By "cryomilling" is meant a reduction in size by homogenizing or pulverizing the tissue in the presence of liquid nitrogen or other such solution to cause the tissues to remain in a frozen state during the homogenizing or pulverizing process."*

The definition is clear in scope and meaning and is thus not indefininte. Reconsideration and withdrawal of the rejection is respectfully solicited.

Further with respect to claim 21, the Examiner considered the language "altering the condition of the in situ tissue" and "effective amount of a dispersed collagen matrix being at the site of the in situ tissue" to be unclear.

Received from < 4012734447 > at 5/8/03 1:36:04 PM [Eastern Daylight Time]

Corrections have been made to claim 21 to address the noted issues. Reconsideration and withdrawal of the rejection is solicited.

Finally, with respect to claims 28-31 and 33-36, the Examiner considers "tryspin resistance" as indefinite.

Claims 28-31 and 33-36 have been amended as suggested by the Examiner. Reconsideration and withdrawal of the rejection is solicited.

Claim Rejections under 35 USC §102:

Claims 33-36 were rejected under 35 USC §102 as being anticipated by Kelman USP 5332802.

The claims are drawn to an injectable composition containing a dispersed dermal tissue matrix having a defined resistance to trypsin.

Kelman discloses an injectable composition comprising an acylated dispersed dermal tissue matrix. As a basis for the rejection, the Examiner states that "The dermal tissue in the composition of Kelman inherently [emphasis added] has a trypsin resistance of greater than 90% as presently claimed."

Applicant respectfully disagrees. Kelman discloses a process for preparing the collagen materials. However, there is no suggestion or discussion whatsoever of trypsin resistance. The Examiner suggests that trypsin resistance is inherent, but this is not the case. In fact, it was a lack of trypsin resistance of the material produced by the Kelman process that led to the development of the current methods as claimed. The Kelman process was used in the production of a commercial product known as Dermalogen. Dermalogen was initially ineffective and failed commercially because the material suffered from excessive trypsin digestion. The improvements in the process as detailed herein increased trypsin resistance and permitted Dermalogen to be commercially successful.

Kelman discloses a method of acylating the collagen material to achieve complete solubilization and thus achieve the ability to inject the material into tissue.

Received from < 4012734447 > at 5/8/03 1:36:04 PM [Eastern Daylight Time]

> *"It is among the objects of this invention to produce a chemically modified, crosslinkable, telopeptide-containing, naturally crosslinked, solubilized collagenous substance obtained directly from intact human tissue from a sole donor, for altering the condition of in situ tissue of the same donor, e.g. for augmenting soft tissue, by autoimplantation." Column 3, lines 18-25.*

The major emphasis of the process was to achieve complete solubilization for injection into human tissue.

Kelman does not contemplate decellularization since the implanted material is intended to be autologous.

> *"Briefly, this invention concerns the processing of collagens from a biopsy or other specimen of human skin or other human tissue (e.g. skin or bone for Type I fibrous collagen, or cartilage for Type II collagen), for use as a biological autoimplant in the same tissue donor alone."* Column 3, lines 26-31.

Kelman includes cryopulverization of the tissue material. However, cryopulverization was introduced to help speed acylation of the tissue.

> *"The total quantity of acylating agent added depends on the extent of disruption, modifying and extracting of the telopeptide collagen desired. For instance, one addition at 150 mg agent per gram of wet tissue may not be sufficient to disperse and solubilize totally the collagen content of the tissue; as many as four such additions may be required.*
>
> *The quantity required should generally satisfy the weight ratio of acylating agent to wet tissue of broadly 0.005-0.5:1, and preferably 0.05-0.1:1.*
>
> *The reaction time for achieving complete solubilizing of the collagenous tissue may range from about 30 minutes to 2 hours. The time depends on the quantity of solubilizing agent, specific solubilizing agent used, rate of agitation or stirring,*

Received from < 4012734447 > at 5/8/03 1:36:04 PM [Eastern Daylight Time]

> *temperature, pH, and degree to which the tissue was initially pulverized or dispersed in the preliminary homogenization treatment." Column 7, lines 44-64.*

The Examiner notes Applicant's statement that "Cryomilling alone produced significant improvements in product yield and resistance to trypsin". However, this must be taken in the context of the paragraph as a whole and the test results from which the statement was gleaned.

> *Results show that the addition of cryomilling and a reduction in the concentration of acylating agent greatly improve dispersed matrix yield and resistance to digestion by trypsin. Cryomilling alone produced significant improvements in product yield and resistance to trypsin. Reductions in the ratio of acylating agent to wet tissue had little effect on milled tissue yield. However, trypsin resistance was increased as shown in Table 1. Paragraph [0051].*

The introduction of cryomilling alone only increased trypsin resistance from 54% to 58% (10% increase). However, the combination of cryomilling and lower acylating agent increased the trypsin resistance from 54% to 70% (close to 50% increase). Similar results can be seen in Table 4.

In the context of the present invention, cryomilling has been found to be an important process step to improve yields, particularly when using the small amounts of acylating agent as disclosed. Cryomilling itself is not sufficient to product high yields of dispersed tissue injectable through a 30G needle. Dispersion of the tissue occurs as the acylating agent reacts with deprotonated proteins, such as collagen. The reaction is rapid and produces a change in net charge on the tissue. As the net charge becomes more negative, certain proteins, (like collagen) and other macromolecules (such as decorin) become more soluble, resulting in a loosening of the matrix. This is followed by more maceration that disperse the once intact tissue into an injectable form. It would not have been obvious to use cryomilling to increase surface area to make the acylating reaction more effective. Cryomilling was not introduced to

Received from < 4012734447 > at 5/8/03 1:36:04 PM [Eastern Daylight Time]

disperse the tissue but to increase surface area so that the acylating agents would be more effective at lower concentrations.

The Examiner also seems to suggest that treatment with glutaric anhydride may yield different results than treatment with succinic anhydride. While we have no comparative data, it is unlikely that there will be any difference in trypsin resistance and dispersed tissue yields when using these two anhydrides. In fact, the chemistry is identical and both compounds are in a similar class of anhydrides.

Turning back to Kelman, the minimum concentration of acylating agent was described in Kelman as 0.005:1 or 0.5%, which is 60% greater than currently specified in the claims, i.e. 0.3% or less. Furthermore, the acylation time was identified as 30 minutes to 2 hours. Acylation time in the present description is identified as 30 seconds to 10 minutes. Even further still, up to four additions of the acylating agent were contemplated in Kelman.

It is thus clear that the intention of Kelman was to entirely disperse and solubilize the collagen material for implantation. No consideration was given to the effect of acylation on trypsin resistance.

Back to the current rejection, i.e. the Examiner states that trypsin resistance is inherent in the Kelman materials. Kelman does not discuss or suggest trypsin resistance whatsoever and there is no basis for inferring that the Kelman materials are trypsin resistant. In fact, the test results as disclosed in the present application contradict this conclusion. Referring to Table 1, a reduction in the amount of acylation agent from 0.20% to 0.16% increased trypsin resistance from 58% to 70%.

Accordingly, it can only be inferred that the increased percentage of acylating agents used in Kelman would further degrade trypsin resistance rather than give it a 90% trypsin resistance.

Reconsideration and withdrawal of the rejection is respectfully solicited.

Claim Rejections under 35 USC §103:

Claims 1-36 were rejected under 35 USC §103(a) as being obvious in view of Kelman.

The Examiner stated that when carrying out the process of Kelman it would have required only limited routine experimentation and been obvious to select a preferred optimum

Received from < 4012734447 > at 5/8/03 1:36:04 PM [Eastern Daylight Time]

amount of acylating agent to use for a particular acylating agent. Kelman et al used an amount of acylating agent to totally disperse and solubilize the collagen content of the tissue. When less than total dispersion is sufficient, it would have been obvious to use lower amounts.

Applicant disagrees, as this is an overly simplistic statement. Kelman discloses a broad range of acylating agent ranging from a minimum of 0.005:1 to about 0.5:1. The fact that Kelman discloses a lower limit of 0.005:1 specifically teaches that Kelman did not believe a processing range below 0.005:1 was possible or for that matter desirable. According to the Examiner's position, it can be inferred that an amount of acylating agent at or above the lower limit of 0.005:1 would be used when less than total dispersion was desired, and not an amount below 0.005:1 as claimed.

The Examiner also states that there is inadequate evidence to establish that using 0.3% provides results significantly different than when using 0.5% as disclosed by Kelman. However, the test results as set forth in the present application contradict this assertion. The stark increase in trypsin resistance between 0.2% and 0.16% is clearly indicative that there is a direct and significant correlation between trypsin resistance and small changes in acylating agent. Furthermore, it is believed that there is a critical upper limit of acylating agent wherein trypsin resistance will be very low no matter how much acylating agent has been used. For example, it is believed that trypsin resistance would be very low for any use of acylating agent over 0.4%. Accordingly, there is believed to be sufficient evidence to establish that using 0.3% or less acylating agent provides significantly improved results.

Reconsideration and withdrawal of the rejection is respectfully solicited.

Claims 1-36 were rejected under 35 USC §103 as being unpatentable over Abraham et al, or Livesay et al, or Goldstein in view of Kelman.

Abraham, Livesay and Goldstein each disclose methods of producing decellularized tissue for implant. The Examiner states that it would have been obvious to treat the decellularized tissue of Abraham, Livesay or Goldstein with an acylating agent as disclosed in Kelman to solubilize the collagen.

Received from <4012734447> at 5/8/03 1:36:04 PM [Eastern Daylight Time]

In light of the above-noted remarks with respect to Kelman, this rejection is no longer believed to be applicable. Because Kelman does not disclose the use of acylating agents in the amounts currently claimed, the combination of Kelman with Abraham or Livesay or Goldstein does not provide the invention as claimed.

Reconsideration and withdrawal of the rejection is respectfully solicited.

CONCLUSIONS:

It is thus the combination of cryomilling the material, i.e. reducing it particle size and increasing its surface area, along with a reduction in the amount of acylating agent that produces the best results, i.e. improved yield along with improved trypsin resistance

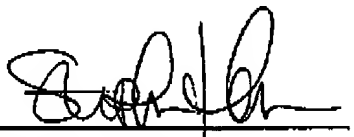
Claims 1, 3-31 and 33-36 are believed to define patentable subject matter over the cited prior art of record.

It is therefore submitted that claims 1, 3-31 and 33-36 are in condition for allowance and the application ready for issue.

Corresponding action is respectfully solicited.

PTO is authorized to charge any additional fees incurred as a result of the filing hereof or credit any overpayment to our account #02-0900.

Respectfully submitted,



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